## REMARKS

Claims 1-41 and 64-69 are currently pending. Claim 70 has been added. Claims 2, 3, 11-15, 18, 21, 22, 27-30, 66-69 have been withdrawn from consideration. Claims 42-63 have been cancelled. Applicants reserve the right to prosecute the subject matter of the withdrawn and cancelled claims in one or more continuation, continuation-in-part, or divisional applications.

Claims 1, 20, 25, 26, 38, 40, and 64 have been amended. These amendments are supported throughout the instant specification. (*See* numbered paragraphs 11-12, 19 21, 23, 27, 31, 38, and 39 of the filed specification.) These amendments are presented in order to further clarify the claimed invention.

Claim 10 has been rejoined to this application because it was withdrawn by the Examiner in the Office Action dated February 8, 2007 in error. In this Office Action the Examiner stated that certain claims (namely claims 2, 3, 10-15, 18, 21, 22, 27-30, and 66-69) were withdrawn as being drawn to nonelected species. However, claim 10 covers a species that was elected in response to the Restriction Requirement dated June 28, 2006. In applicants' response to this Restriction Requirement which was submitted on July 26, 2006, three species were elected: (1) an encapsulated agent, (2) an ***intracellular inhibitor***, and (3) a bisphosphonate. The Examiner acknowledged this election as proper in the Office Action dated February 8, 2007, however at the same time the Examiner also withdrew claim 10 which is directed to an agent that is an ***intracellular inhibitor***. Therefore, applicants believe claim 10 is properly to be considered part of the elected group and species.

Claim 70 has been added to this application. Support for this claim is found in numbered paragraphs 15, 27, and 39 of the filed specification. No new matter is introduced by this added claim.

## Response to 35 U.S.C. §103(a) Rejections

***Hope, et al.***

Claims 1, 6-9, and 20 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Hope, et al. (U.S. 6,139,871). Applicants respectfully disagree with this rejection.

MPEP 2141.02 states that the prior art reference must be considered in its entirety including portions that would lead away from the claimed invention. Applicants assert that the instant claims are not rendered obvious by Hope, et al. because this prior art reference teaches away from the claimed invention.

The Examiner contends that Hope teaches encapsulated agents such as liposomes. Applicants respectfully disagree with this position. Liposomes are not "encapsu*lated* agents" but are instead "encapsu*lation* agents," *i.e.*, they can serve as vehicles to encapsulate other agents to make a "formulation," which as a formulation is capable of acting in the claimed method. Applicants have amended the claims to clarify this fundamental distinction. In contrast to the instant claims, Hope defines "liposome," "vesicle," and "liposome vesicle" as structures having lipid-containing membranes enclosing an aqueous interior. (*See* col. 5, lines 1-3.) Hope specifically states that their liposomes "are not bound to a *drug*." (*See* col. 3, lines 65 - col. 4, line 1; col. 4, lines 55-59; and col. 5, lines 34-38.) Hope defines "drug" as a "synthetic compound suitable for therapeutic use without associated bound carriers, adjuvants, activators, or co-factors." (*See* col. 4, lines 62-64.) Throughout the specification, Hope repeats that their liposomes should not be combined with "drugs." (*See* col. 4, lines 1-2 and 62-64; col. 5, lines 34-38.) This concept of treating a patient with an empty liposome, *i.e.*, one containing no drugs or therapeutic agent, teaches away from the instant claims which are directed to a method of treating a patient using a formulation comprising a therapeutic agent encapsulated within a suitable carrier. The instant specification defines "agent" as "any substance that once released within the targeted macrophages/monocytes inhibits and/or destroys the macrophages and monocytes to minimize myocardial necrosis." (*See* paragraph 28, page 7 of the instant specification.)

Thus, the instant claims combine the liposome with a "drug" or therapeutic agent which is in contrast to the teaching of Hope.

Further, applicants assert that the instant claims operate in a completely different manner than those described by Hope. Hope describes the use of empty liposomes to remove cholesterol by binding cholesterol to the liposomes for clearance by the hepatocytes in the liver. (*See* col. 3, lines 51-53; col. 5, lines 14-33; and col. 7, lines 31-52.) In contrast, the instant claims use a suitable carrier, such as a liposome, to make a formulation (*i.e.*, a therapeutic agent and a carrier) which specifically targets phagocytic cells for destruction. (*See* pages 6-7, paragraphs 24-27 of the instant specification.) Hope does not teach or suggest the combination of a therapeutic compound in a liposome (or other suitable carrier) to make a formulation capable of treating an acute myocardial infarction.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) as to claims 1, 6-9, and 20 are respectfully requested for the above reasons and claim amendments.

***Ylitalo in view of Hope, et al.***

Claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-38, 40, 41, 64, and 65 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Ylitalo (*Gen. Pharmacol.*, 35:287-296, 2002) in view of Hope, et al. (U.S. 6,139,871). Applicants respectfully disagree with this rejection.

The Examiner contends that these two references, Ylitalo and Hope, each teach elements of the instant claims and therefore the combination of these references make the instant claims obvious. Applicants respectfully disagree with this rejection.

As mentioned above, Hope describes a method of treating atherosclerosis using liposomes which are devoid of any additional "synthetic compound suitable for therapeutic use without associated bound carriers, adjuvants, activators, or co-factors." (*See* col. 4, lines 62-64). In contrast, Ylitalo describes the use of bisphosphonates, a synthetic compound suitable for therapeutic use (*i.e.*, a "drug" as defined by Hope) without any encapsulation in a carrier (*i.e.*, no liposome), to treat atherosclerosis. Ylitalo

does not describe the use of liposome-encapsulated bisphosphonates for the treatment of atherosclerosis as the Examiner asserts. The main thrust of Ylitalo describes the use of naked (*i.e.*, un-encapsulated) bisphosphonates for the treatment of calcification, wherein one such use is the calcification of arteries. One paragraph on page 293, col. 2, last paragraph, describes the inhibition of iodinated LDL uptake in macrophage cells *in vitro* by bisphosphonate in liposomes. The authors do not use this *in vitro* study to suggest that liposome bisphosphonates are effective treatment for atherosclerosis, let alone for acute myocardial infarction. In fact, throughout the publication, Ylitalo indicates that free bisphosphonates are sufficient for effective treatment of atherosclerosis and that liposomes are unnecessary for effective treatment of atherosclerosis. Moreover, these two references are not properly combinable because Hope teaches away from their combination. MPEP 2145 states that "[i]t is improper to combine references where the references teach away from their combination." (*See* MPEP 2145, citing *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).) As discussed *supra*, Hope affirmatively teaches away from using a "drug" or therapeutic agent in combination with a liposome. (*See* Hope, col. 3, lines 65 - col. 4, line 2; col. 4, lines 55-59; col. 4, lines 62-64; and col. 5, lines 34-38.)

More importantly, neither Ylitalo nor Hope teach or suggest a method of treating acute myocardial infarction. At best, one skilled in the art might consider using empty liposomes or free bisphosphonates to treat atherosclerosis in view of these two references, but there is no common sense reason to combine these therapies. Neither reference alone or in combination teach or suggest to use of a combination formulation as claimed for the treatment of an acute myocardial infarction.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) as to claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-38, 40, 41, 64, and 65 are respectfully requested for the above reasons and claim amendments.

***Golomb, et al. (U.S. 6,719,998) in view of Hope, et al.***

Claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64, and 65 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Golomb, et al. (U.S. 6,719,998) in view of Hope, et al. (U.S. 6,139,871). The Examiner contends that one skilled in the art would

take the teachings of Golomb and apply the treatment to patients suffering from acute myocardial infarction in order to treat the zone of infarct. Applicants respectfully disagree with this rejection.

As discussed above, Hope is specifically directed to a treatment for atherosclerosis and not an acute myocardial infarction. Also, as discussed above, Hope treats atherosclerosis with empty liposomes, *i.e.*, ones that DO NOT CONTAIN ANY DRUGS. The instant claims are directed to a treatment for acute myocardial infarction and use a formulation containing BOTH a therapeutic agent and a suitable carrier. Hope does not teach or suggest any of these elements of the claims.

Golomb describes a composition having a pharmaceutically active ingredient (*i.e.*, a prohibited "drug" as defined by Hope) for the prevention or treatment of vascular restenosis. (*See* col. 3, lines 1-7; and col. 4, lines 14-24.) Golomb does not teach or suggest that encapsulated bisphosphonates can be useful in a method of treating an acute myocardial infarction or reducing the zone of infarct as claimed.

Golomb describes a treatment for restenosis, a condition that is the direct result of an angioplasty procedure in a blood vessel. The Examiner contends that since restenosis implies that a stenosis had previously occurred, one skilled in the art would use the teachings of these references to treat an acute myocardial infarction. (*See* page 8 of the September 7, 2007 Office Action.) Applicants respectfully disagree and assert that the Examiner has employed impermissible hindsight in applying these references to the treatment of acute myocardial infarction and the accompanying zone of infarct. Just because a liposomal bisphosphonate can be used to treat restenosis does not mean that it will have any effect on a patient in the midst of an acute myocardial infarction or treat the resulting permanent damage to the myocardium. Unlike the formulation of the present invention, once an acute myocardial infarction begins, medicines known in the art to prevent its occurrence will have no effect in stopping the event or preventing the resulting damage to the myocardium. Neither reference, Golomb nor Hope, teach or suggest that the use of a formulation containing a therapeutic agent in a suitable carrier can be used to treat myocardial damage at the zone of infarct. As discussed *supra*, neither Golomb nor Hope teach this element of the

instant claims and their combination is not proper since Hope teaches away from combining "drugs" or therapeutic agent with a liposome (or other suitable carrier).

Further, applicants assert that one skilled in the art would not use the teaching of Golomb to treat acute myocardial infarctions. Golomb's disclosure can be analogized with the non-effectiveness of lowering a patient's cholesterol for treating a zone of infarct. Reducing a patient's cholesterol may reduce plaque build-up, which is responsible for vessel obstruction, which may possibly lead to ischemia and, more remotely to an acute myocardial infarction. However, lowering a patient's cholesterol will not reduce the zone of infarct due to acute myocardial damage caused by the acute infarction. Once an acute myocardial infarction has started to occur, administering a cholesterol-lowering drug will not stop the acute infarction from occurring, nor will it treat the damage to the myocardium which will result from the acute event. In other words, while lowering a patient's cholesterol is good to prevent a series of events or a downstream event from eventually happening (*i.e.*, a possible acute myocardial infarction), lowering the cholesterol will have no effect on a patient when he is suffering from a heart attack. The instant claims are directed to "treating" an acute myocardial infarction (*i.e.*, a heart attack). The use of the word "treating" indicates that the event has already occurred or is known to be imminent (*i.e.*, the patient is undergoing an angioplasty or other procedure likely to trigger acute myocardial infarction).

Similarly, once a zone of infarct has been created, one skilled in the art would have no reason to apply the teachings of Golomb, alone or in combination with Hope, to treat the damage or to prevent further damage of the myocardium. It requires a separate invention to arrive at the instant claims; one that is not taught or suggested by the teachings of Golomb, alone or in combination with Hope.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) as to claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64, and 65 are respectfully requested for the above reasons and claim amendments.

***Golomb, et al. (U.S. 6,984,400) in view of Hope, et al.***

Claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64, and 65 have been rejected under 35 U.S.C. §103(a) as obvious over Golomb, et al. (U.S. 6,984,400) in view of Hope, et al. (U.S. 6,139,871). Applicants respectfully disagree with this rejection.

The combination of Golomb (U.S. 6,984,400) (hereinafter the "'400 Golomb reference") and Hope is not proper because Hope teaches away from the use of therapeutic agents in a suitable carrier. The '400 Golomb reference describes a composition having a pharmaceutically active ingredient (*i.e.*, a "drug" as defined by Hope) for treating restenosis. (*See* columns 2 and 3.) Again, Hope teaches away from Golomb because Hope teaches using empty liposomes (*i.e.*, ones that do NOT contain any therapeutic compounds). The '400 Golomb reference fails to teach or suggest a method of treating an acute myocardial infarction or reducing the zone of infarct as claimed in the instant invention. As discussed above, a useful method of treating restenosis is by no means automatically a useful treatment for acute myocardial infarction once it has occurred.

The Examiner repeats the contention that one skilled in the art would take the teachings of Golomb ('400) and apply the treatment to patients suffering from acute myocardial infarction in order to treat the zone of infarct. Applicants respectfully disagree. Golomb ('400) describes a treatment for restenosis, a condition associated with angioplasty procedures. Neither the Golomb ('400) nor the Hope reference, teach or suggest treating a zone of infarct. As discussed above, just because liposomal bisphosphonate can be used to treat restenosis, a condition that *may* lead to an acute myocardial infarction over time, does not mean that it will treat an acute myocardial infarction or treat the resulting permanent damage of myocardium. As previously stated, it requires a separate invention to arrive at the instant claims; one that is not taught or suggested by the teachings of Golomb ('400), alone or in combination with Hope.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) as to claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64, and 65 are respectfully requested for the above reasons and claim amendments.

***Golomb, et al. (U.S. 7,008,645)***

Claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64, and 65 have been rejected under 35 U.S.C. §103(a) as being obvious over Golomb, et al. (U.S. 7,008,645). Applicants respectfully disagree with this rejection.

The Examiner contends that these two references, Golomb ('645) and Hope, each teach elements of the instant invention and therefore the combination of these references make the instant invention obvious. Once again, applicants assert that these two references are not properly combinable because Hope teaches away from their combination. Golomb ('645) describes administering bisphosphonate (*i.e.*, a drug as defined by Hope) for the prevention or treatment of restenosis. (*See* col. 3, lines 1-7; and col. 4, lines 14-24.) As described *supra*, Hope teaches away from the use of drugs in a liposome and thus teaches away from its combination with Golomb ('645). Further, Golomb ('645) does not teach or suggest a method of treating an acute myocardial infarction or reducing the zone of infarct as claimed.

The Examiner again repeats the contention that one skilled in the art would take the teachings of this Golomb reference and apply the treatment to patients suffering from acute myocardial infarction in order to treat the zone of infarct. Applicants respectfully disagree and maintain the position set forth above. Golomb ('645) discloses a treatment for restenosis, a condition associated with angioplasty procedures. Again, simply because a treatment may be useful to treat restenosis does not mean that it will have any effect on a patient having an acute myocardial infarction or treat the resulting permanent damage to the myocardium. Treating restenosis is a measure designed to prevent the build-up of scar-tissue in the blood vessel. It is not effective at treating a patient who is suffering from an acute myocardial infarction which occurs when the blood supply to a part of the heart is interrupted resulting in ischemia or oxygen shortage causing damage and potential death of heart tissue. It requires a separate invention to arrive at the instant invention; one that is not taught or suggested by the teachings of Golomb ('645), alone or in combination with Hope.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) as to claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64, and 65 are respectfully requested for the above reasons and claim amendments.

## CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the rejections of the pending claims and request allowance of this application.

## AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-4387**, Order No. **92114.005US1**.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-4387**, Order No. **92114.005US1**.

Respectfully submitted,
CADWALADER, WICKERSHAM & TAFT LLP

Dated: January 7, 2008

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